pharmacological effects compel continued use. These widely disseminated public findings establish that a reasonable person in the position of a tobacco manufacturer would foresee that tobacco products would be consumed to satisfy an addiction to nicotine.[159]

4. It Is Foreseeable That Consumers Will Use Cigarettes and Smokeless Tobacco for Other Pharmacological Purposes

In addition to its foreseeable addictive effects, nicotine produces a range of other well-known and foreseeable significant pharmacological effects of importance to tobacco users. Evidence demonstrating that consumers actually use tobacco products for these effects is discussed in section II.B.2., below.

Central Nervous System Effects: Sedation, Stimulation, Mood, and Cognition. Nicotine significantly alters the structure and function of the brain. At the molecular level, nicotine acts by stimulating receptors on the surfaces of brain cells intended for natural neurotransmitters such as acetylcholine and by stimulating the release of other key substances such as dopamine.[160] Nicotine also changes the brain's molecular structure. Extensive animal research by both the tobacco industry and other researchers shows that nicotine exposure, ranging from a few days to a few weeks, within the range of doses equivalent to those received from smoking cigarettes, increases the number and changes the functional activity of nicotine receptors in the brain.[161] In one study, doses of nicotine

[159] FDA notes that at least one major tobacco company appears to agree that information about the "addicting" properties of cigarettes is so widely disseminated that it must be considered foreseeable. In a lawsuit brought against RJR by a smoker, RJR argued that the "alleged habitutating or 'addicting'" qualities of cigarette smoking are so well known that smokers must be held to have foreseen them. *See* section II.C.2.b.iv., below.

[160] *See* the discussion of dopamine in the mesolimbic system, section II.A.3.c.i., above.

[161] Marks MJ, Burch JB, Collins AC, Effects of chronic nicotine infusion on tolerance development and nicotine receptors, *Journal of Pharmacology and Experimental Therapeutics* 1983;226:817-825. *See* AR (Vol. 41 Ref. 103).

considered equivalent to those received by a fetus of a smoking mother increase the number of nicotine receptors in the brains of newborn rats.[162] Consistent with animal data, cigarette smokers show clear evidence of increased numbers of cerebral nicotine receptors as a consequence of their smoking.[163]

The result of these molecular actions is that nicotine clinically affects arousal, attention, mood, and, under certain conditions, cognition. Depending on the dose and the circumstances, nicotine delivered by cigarette smoking can have an arousal-increasing or arousal-reducing effect.[164] This is another respect in which nicotine is similar to such other addictive drugs as opiates, which can have both stimulating and sedating effects.

Nicotine's effects on mood and arousal have been confirmed using electroencephalographic (EEG) analysis, a measurement of electrical activity in the brain.[165] When smokers are placed in a stressful situation, smoking can have a depressant

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Surgeon General's Report, 1988, at 53-54. *See* AR (Vol. 129 Ref. 1592).

Department of Health and Human Services, Office on Smoking and Health, *Preventing Tobacco Use Among Young People: A Report of the Surgeon General* (Washington DC: GPO, 1994), at 32-33. *See* AR (Vol. 133 Ref. 1596).

[162] Slotkin TA, Orband-Miller L, Queen KL, Development of (^{3}H)nicotine binding sites in brain regions of rats exposed to nicotine prenatally via maternal injections or infusions, *Journal of Pharmacology and Experimental Therapeutics* 1987;242:232-237. *See* AR (Vol. 140 Ref. 1656).

[163] Benwell MEM, Balfour DJK, Anderson JM, Evidence that tobacco smoking increases the density of (–)-[^{3}H]nicotine binding sites in human brain, *Journal of Neurochemistry* 1988;50:1243-1247. *See* AR (Vol. 136 Ref. 1570).

[164] Norton R, Brown K, Howard R, Smoking, nicotine dose and the lateralisation of electrocortical activity, *Psychopharmacology* 1992;108:473-479. *See* AR (Vol. 3 Ref. 22).

[165] Pritchard WS, Gilbert DG, Duke DW, Flexible effects of quantified cigarette-smoke delivery on EEG dimensional complexity, *Psychopharmacology* 1993;113:95-102. *See* AR (Vol. 3 Ref. 23-1).

Pritchard WS, Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490. *See* AR (Vol. 105 Ref. 965).

effect on the EEG profile.[166] When smokers are placed in conditions of low arousal induced by mild sensory isolation, cigarette smoking can have a stimulant effect.[167] In other words, smoking can have a relaxing effect in stressful situations and a stimulating effect in otherwise nonstimulating circumstances.

The tobacco industry correctly observes that many substances affect the EEG. But what is significant is not *that* nicotine affects the EEG, but *how* nicotine does so. Nicotine's impact on the EEG: (1) is reproducible, (2) is clinically significant, (3) corresponds to other physiological and psychological changes of smoking, and (4) is similar to certain EEG changes associated with other addictive drugs such as benzodiazepines.[168] Altered electrical activity of the brain as demonstrated by EEG is convincing evidence of nicotine's significant pharmacological effects on the structure and function of the body.

Smokers perform better on some cognitive tests than do deprived smokers, but nicotine does not improve general learning or make smokers generally perform better than nonsmokers.[169] One leading researcher noted that, after a few hours of abstinence, "[P]eople are reporting they can't concentrate as well, they can't get the tasks done as

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Golding JF, Effects of cigarette smoking on resting EEG, visual evoked potentials and photic driving, *Pharmacology, Biochemistry and Behavior* 1988;29:23-32. *See* AR (Vol. 3 Ref. 23-3).

[166] Pritchard WS, Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490. *See* AR (Vol. 105 Ref. 965).

[167] Golding J, Mangan GL, Arousing and de-arousing effects of cigarette smoking under conditions of stress and mild sensory isolation, *Psychophysiology* 1982;19(4):449-456. *See* AR (Vol. 48 Ref. 101).

[168] Pritchard WS, Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490, at 485, 488. *See* AR (Vol. 105 Ref. 965).

[169] Surgeon General's Report, 1988, at 441. *See* AR (Vol. 129 Ref. 1592).

well, and our objective performance batteries confirm that. They're right . . . it's not just a psychological effect. They really aren't functioning as well."[170]

Evidence on nicotine's effects on mood and cognition is strongly supported by the work of tobacco industry researchers, who concur that people use tobacco for the psychoactive effects of nicotine. These researchers contend that nicotine delivered by tobacco produces psychoactive effects comparable to the effects of prescription tranquilizers. For example, a researcher for the R.J. Reynolds Tobacco Company (RJR), W. S. Pritchard, reported that smoking cigarettes could produce "an EEG effect that in the benzodiazepine literature is associated with anxiety relief," leading him to conclude that "an important smoking motive for deep inhaling smokers might be anxiety reduction" and that his results were consistent with the theory that smoking provides beneficial psychological effects ("psychological tools" or "resources").[171]

In a significant extension of this work, Robinson *et al.* concluded that "the beneficial effects of smoking on cognitive performance are a function of nicotine absorbed from cigarette smoke upon inhalation."[172] These RJR researchers performed their study because they thought that, although earlier work with various nicotine preparations was consistent with the hypothesis that people smoked for "psychopharmacological effects,"

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[170] Henningfield J, Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), at 309. *See* AR (Vol. 255 Ref. 3445).

[171] Pritchard WS, Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490, at 485, 488. *See* AR (Vol. 105 Ref. 965).

[172] Robinson JH, Pritchard WS, Davis RA, Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine, *Psychopharmacology* 1992;108:466-472. *See* AR (Vol. 59 Ref. 236).

the role of nicotine in cigarettes was inconclusive. They therefore compared standard nicotine-delivering cigarettes to cigarettes that were similar in all other relevant characteristics (e.g., similar gases, tar, etc.) but that provided only "trace" or "minimal" levels of nicotine. The regular cigarettes provided psychopharmacological effects, while the minimal nicotine cigarettes did not.

One of the leading tobacco industry-funded proponents of the contention that nicotine is not addictive, D. M. Warburton, is also one of the leading proponents of the view that people smoke because of the pharmacological actions of nicotine in the brain, rather than in the mouth.[173] Warburton argues that nicotine is a "therapeutic agent" that is self-administered by smokers to "control their bodily state"[174] and that "the rapid absorption and rapid metabolism make this substance suitable for hour-by-hour self-medication because of the personal control [over dosage needs] that can be exercised. In this respect nicotine is superior to other compounds for medication."[175] Thus, the conclusions of tobacco industry-funded researchers support FDA's finding that a reasonable manufacturer would foresee that nicotine in tobacco products produces significant pharmacological effects important to users.

Other Effects: Weight Regulation. Nicotine also plays a role in weight regulation. The 1988 Surgeon General's Report summarized the available data:

> In summary, there is substantial evidence of an inverse relationship between cigarette smoking and body weight. Of 71 studies reported since 1970, 62 (87%) collectively indicate that smokers

[173] Warburton DM, Nicotine: an addictive substance or a therapeutic agent, *Progress in Drug Research* 1989;33:9-41. *See* AR (Vol. 140 Ref. 1657).

[174] *Id.* at 11.

[175] *Id.* at 37.

> weigh less than nonsmokers and that people who quit smoking gain weight. . . .
>
> Animal studies indicate that nicotine administration results in weight loss or decreased weight gains and that cessation of nicotine results in body weight gains greater than those of controls [animals that did not receive nicotine]. . . .
>
> Recent research on nicotine polacrilex gum with humans corroborates the role of nicotine in body weight effects.[176]

Numerous studies show that many tobacco consumers use tobacco to control their weight. For example, in two surveys, between one-third and one-half of young people reported that controlling weight was one of their reasons for smoking.[177]

An extensive discussion of the physiological and central nervous system effects of nicotine is available in the 1988 Surgeon General's Report.[178]

Thus, aside from addiction, there are other foreseeable pharmacological effects of nicotine use that are important to users; that these effects are actual reasons for consumption is discussed in section II.B.3., below.

5. Cigarettes and Smokeless Tobacco Deliver Pharmacologically Active Doses of Nicotine

Currently marketed cigarettes and smokeless tobacco deliver sufficient doses of nicotine to cause addiction and lead to other significant pharmacological effects that cause continued use of the products. This robust conclusion is supported by published research presented in section II.A., above, and thus is foreseeable to a reasonable tobacco manufacturer. For example, laboratory studies using commercial cigarettes demonstrate that the products contain pharmacologically active levels of nicotine; epidemiological data

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[176] Surgeon General's Report, 1988, at 431-432. *See* AR (Vol. 129 Ref. 1592).

[177] *Id.* at 438-440.

[178] *Id.* at 381-458.

show that actual tobacco consumers do become addicted. Four additional types of evidence conclusively demonstrate that tobacco products deliver sufficient doses of nicotine: (1) measurements of blood nicotine levels after consumption of tobacco products; (2) laboratory studies using doses of nicotine that are equivalent to those imparted by tobacco use; (3) studies demonstrating that nicotine levels control tobacco consumption behavior (known as "compensation"); and (4) studies of nicotine replacement therapy.

Measurement of Blood Nicotine Levels. Evidence demonstrates that tobacco users receive pharmacological doses of nicotine when they consume cigarettes and smokeless tobacco. A currently marketed cigarette typically delivers about 1 mg of nicotine to the bloodstream of a smoker,[179] with individual intake ranging from 0.3 to 3.2 mg of nicotine per cigarette.[180] Studies have also revealed that, with regular use throughout the day, the levels of nicotine in the blood of smokeless tobacco users are similar to those observed in cigarette smokers. Data demonstrating that these products deliver substantial, pharmacologically active doses of nicotine are summarized in the Jurisdictional Analysis. *See* 60 FR 41571–41575.

Laboratory Studies. Long before evidence emerged that nicotine is addictive, studies demonstrated that the quantitative and even qualitative nature of the effects of

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[179] Benowitz NL, Henningfield JE, Establishing a nicotine threshold for addiction, *New England Journal of Medicine* 1994;331:123-125. *See* AR (Vol. 12 Ref. 130).

Gori GB, Lynch CJ, Analytical cigarette yields as predictors of smoke bioavailability, *Regulatory Toxicology and Pharmacology* 1985;5:314-326. *See* AR (Vol. 12 Ref. 142).

[180] Benowitz NL, Henningfield JE, Establishing a nicotine threshold for addiction, *New England Journal of Medicine* 1994;331:123-125. *See* AR (Vol. 12 Ref. 130).

nicotine were dependent on the dose.[181] In the 1980's, particularly important discoveries provided indisputable proof that the nicotine dose levels produced by cigarette smoking affect the structure and function of the body, and that many of these effects are similar to those of prototypic addictive drugs. For example, nicotine, administered in doses considered biologically equivalent to those from tobacco use, was found to affect the brain's use of energy (cerebral glucose utilization).[182] Additionally, nicotine exposure at doses equivalent to those from tobacco use altered the brain so that excess nicotine receptors appeared on the surfaces of brain cells; this structural change was associated with altered responsiveness to nicotine.[183]

In addition, nicotine administered to animals in doses and at intervals comparable to those humans obtain from smoking produces one of the hallmark effects of addictive drugs: brain-mediated reinforcement of self-administration behavior. In the early 1980's, Goldberg and colleagues at Harvard and the National Institute on Drug Abuse provided unequivocal evidence that nicotine in doses comparable to those obtained in humans could

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[181] *See* Surgeon General's Report, 1988, chaps. 2-6. *See* AR (Vol. 129 Ref. 1592).

[182] *Id.* at 85-88.

[183] Marks MJ, Burch JB, Collins AC, Effects of chronic nicotine infusion on tolerance development and nicotine receptors, *Journal of Pharmacology and Experimental Therapeutics* 1983;226:817-825. *See* AR (Vol. 41 Ref. 103).

Surgeon General's Report, 1988, at 53-54. *See* AR (Vol. 129 Ref. 1592).

Id. at 32-33.

Benwell MEM, Balfour DJK, Anderson JM, Evidence that tobacco smoking increases the density of (–)-[^{3}H]nicotine binding sites in human brain, *Journal of Neurochemistry* 1988;50:1243-1247. *See* AR (Vol. 136 Ref. 1570).

function powerfully to engender repetitive drug-seeking behavior in monkeys.[184] In the late 1980's, Corrigall and Coen developed a rat model utilizing key dosing parameters of cigarette smoking and smokeless tobacco use. This model provided for the delivery of very rapid and small doses and led the animals to repeatedly administer nicotine to themselves.[185]

Nicotine Control of Tobacco Use. Nicotine's key pharmacological role in actual tobacco products is also confirmed by evidence that tobacco users adjust their consumption based on the products' nicotine levels. Manipulation of nicotine levels in cigarettes while holding the tar content constant has shown that nicotine is responsible for the maintenance of cigarette smoking behavior. Cigarette smokers given cigarettes with a high nicotine content decrease the number of cigarettes smoked.[186] Modifying the amount of nicotine available by varying the length of cigarette smoked will influence the amount of the cigarette smoked[187] and the characteristics of smoking (e.g., number of puffs, puff duration, puff size, depth of inhalation, amount of tobacco smoked).[188] When cigarettes are shorter,

[184] Goldberg SR, Spealman RD, Goldberg DM, Persistent behavior at high rates maintained by intravenous self-administration of nicotine, *Science* 1981;214:573-575. *See* AR (Vol. 5 Ref. 35-2).

[185] Corrigall WA, Coen KM, Nicotine maintains robust self-administration in rats on a limited access schedule, *Psychopharmacology* 1989;99:473-478. *See* AR (Vol. 347 Ref. 5495).

[186] Goldfarb T, Gritz ER, Jarvik ME, *et al.*, Reactions to cigarettes as a function of nicotine and "tar," *Clinical Pharmacology and Therapeutics* 1976;19:767-772. *See* AR (Vol. 39 Ref. 53).

[187] Jarvik ME, Popek P, Schneider NG, *et al.*, Can cigarette size and nicotine content influence smoking and puffing rates? *Psychopharmacology* 1978;58:303-306. *See* AR (Vol. 41 Ref. 86).

[188] Surgeon General's Report, 1988, at 158-163. *See* AR (Vol. 129 Ref. 1592).

people smoke more of them.[189] Nemeth-Coslett and Griffiths showed that puff duration and puff volume are inversely proportional to the length of the cigarette.[190]

Studies conducted by Stolerman,[191] Nemeth-Coslett *et al.*,[192] and Pomerleau *et al.*[193] provide convincing evidence that tobacco products provide pharmacologically active doses of nicotine. Pretreatment of cigarette smokers with mecamylamine, an antagonist to nicotine that enters the brain, produced a dose-dependent increase in cigarette smoking (i.e., increases in puffs per cigarette, puff duration, and cigarettes per session and decreases in intercigarette interval and interpuff interval) that resembled what one would expect to see if the nicotine dose in the cigarette had been decreased. An increase in nicotine plasma levels also accompanied the increase in cigarette consumption. Pretreatment with another nicotine antagonist that did not enter the brain had no such effects. These studies clearly demonstrate that obtaining a pharmacologically active dose of nicotine in the brain motivates the amount of tobacco consumed on a daily basis.

Evidence from Nicotine Replacement Products. As described in the Jurisdictional Analysis, 60 FR 41565–41566, the ability of nicotine nasal spray to produce some of the classic characteristics of addiction to nicotine supports the position that tobacco users

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[189] Jarvik ME, Popek P, Schneider NG, *et al.*, Can cigarette size and nicotine content influence smoking and puffing rates? *Psychopharmacology* 1978;58:303-306. *See* AR (Vol. 41 Ref. 86).

[190] Surgeon General's Report, 1988, at 161. *See* AR (Vol. 129 Ref. 1592).

[191] Stolerman IP, Goldfarb T, Fink R, *et al.*, Influencing cigarette smoking with nicotine antagonists, *Psychopharmacologia* 1973;28:247-259. *See* AR (Vol. 42 Ref. 149).

[192] Nemeth-Coslett R, Henningfield JE, O'Keffe MK, *et al.*, Effects of mecamylamine on human cigarette smoking and subjective ratings, *Psychopharmacology* 1986;88:420-425. *See* AR (Vol. 41 Ref. 108).

[193] Pomerleau CS, Pomerleau OF, Majchrzak MJ, Mecamylamine pretreatment increases subsequent nicotine self-administration as indicated by changes in plasma nicotine level, *Psychopharmacology* 1987;91:391-393. *See* AR (Vol. 42 Ref. 112).